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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/761,636	01/18/2001	Marc G. Achen	1064/48505	6112

7590 01/22/2004

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EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 01/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/761,636	ACHEN ET AL.	
	Examin r	Art Unit	
	Phuong Huynh	1644	

--The MAILING DATE of this communication appears on the cover sh et with the correspondenc address --

THE REPLY FILED 15 September 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *15 September 2003*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☐ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: *None*.

Claim(s) objected to: *None*.

Claim(s) rejected: *1-3,12,13,18,23,24,26,49-51,53-55,63 and 72-88*.

Claim(s) withdrawn from consideration: *4,14-17,25,52,56-62 and 89-103*.

8.☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☐ Other: _____

Continuation of 3. Applicant's reply has overcome the following rejection(s): The rejection of claims 76-79 under 35 U.S.C. 112, second paragraph is hereby withdrawn.

Continuation of 5. does NOT place the application in condition for allowance because:

The enablement rejection of Claims 1-3, 12-13, 18, 23-24, 26, 49-51, 53-55, 63 and 72-88 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention for the same reasons o record.

Applicants' arguments filed 9/15/03 have been fully considered but are not found persuasive.
Applicants' position is that the law on enablement does not require that all examples are operative. Inoperative embodiments are excluded from the scope of the claimed invention. The discussion on dimeric peptides are irrelevant. The instant application discloses numerous examples and guidance as to how one can arrive at the claimed invention. Only routine experimentation is required to arrive a the claimed monocyclic peptides. All of the claimed peptides as demonstrated by the working examples are based on the loop fragment of the VEGF, VEGF-C or VEGF-D.

In contrast to applicant's continued assertion that the claimed petpides as demonstrated by the working examples are based on the loop fragment of VEGF, and VEGF-C, the specification discloses only monocyclic peptides based on the VEGF-D and not VEGF, or VEGF-C as claimed. In fact, none of the working examples and sequences in the specification as filed demonstrating that the claimed monocyclic peptides are based on VEGF or VEGF-C. The specification does not teach how to make and use any monomeric monocyclic peptide because there is insufficient guidance as to the core sequence which consists of a receptor-binding loop 1, 2 or 3 of any VEGF such as VEGF-C and VEGF-D. Further, there is insufficient guidance as to which amino acids within the undisclsoed core sequence corresponding to which loop fragment can be modified such as substitution, deletion, or insertion and whether the resulting modified monomeric monocyclic peptide will maintain structure and interferes with any biological activity of VEGF, VEGF-C and VEGF-D mediated by VEGF receptor-2 and/or VEGF receptor-3.

The written description rejection of Claims 1-3, 12-13, 18, 23-24, 26, 49-51, 53-55, 63 and 72-88 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention for the same reasons o record.

Applicants' arguments filed 9/15/03 have been fully considered but are not found persuasive.
Applicants' position is the specification describes numerous representatives of this genus of peptides 1, 2 and 3 corresponding to SEQ ID NO: 5, 6 and 7 (monomers) and peptides 4, 5, 6 (dimers). The specification describes how variants of the disclosed core sequences can be obtained by ordinarily skilled person and further provides guidelines as to which specific amino acid residue of the polypeptide are conserved for maintaining a receptor binding activity.

However, the specification discloses only various monomeric monocyclic peptides such as the ones shown in Table 1 on page 32 and Table 2 on page 47 of the specification. However, only three monocyclic peptides (peptides number 1-3), which correspond to SEQ ID NO: 5, 6, 7, respectively, have been demonstrated to inhibit VEGF-DDNDC, VEGF-C, VEGF-D and mouse VEGF164 induced VEGFR-2 and VEGFR-3 mediated cell survival in vitro. Note, none of the monocyclic peptides shown in Table 2 and dimeric bicyclic peptides show in Table 3 were found to inhibit any VEGF, VEGF-DDNDC, VEGF-C, VEGF-D and mouse VEGF164 induced VEGFR-2 and VEGFR-3 mediated cell survival in vitro. The specification further discloses that heterodimeric bicyclic peptide number 5, which corresponds to SEQ ID NO: 8 linked to SEQ ID NO: 9 (Table 1 on page 32) caused a significant reduction in number (Fig 11b). In contrast, neither homodimeric bicyclic peptides 4 and 6, which correspond to SEQ ID NO: 8 linked to SEQ ID NO: 8 or SEQ ID NO: 9 linked to SEQ ID NO 9 caused a significant change in cell number (page 39). None of the dimeric bicyclic peptides mentioned above appear to be more effective inhibitors than the monomeric monocyclic peptides in VEGF-D induced VEGFR-3 cell survival. The specification also discloses that deletion mutant selected from the group consisting of SEQ ID NO: 10, 11 and 12 having one or two internal amino acid deletion or amino acid substitution fail to inhibit the VEGF-DDNDC, VEGF-C, VEGF-D and mouse VEGF164 induced VEGFR-2 and VEGFR-3 mediated cell survival in vitro.

There is inadequate written description about the core sequence which consists of a receptor binding loop 1, 2 or 3 of VEGF, VEGF-C or VEGF-D and which amino acid within said core seqeunce can be substitute for which undisclosed amino acid and which one or two amino acid within said undisclsoed core sequence can be deteled, or inserted and whether the resulting monomeric monocyclic peptide after modification maintains native conformation and interferes with which activity of which VEGF mediated by which VEGF receptors suc as VEGF receptor-2 and/or receptor -3.

The new matter rejection of Claims 1-3, 12-13, 18, 23-24, 26, 63 and 72-88 stands rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevan art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons of record.

Applicants' arguments filed 9/15/03 have been fully considered but are not found persuasive.
Applicants' position is the phrase "a receptor binding loop 1, 2 or 3 of VEGF, VEGF-C or VEGF-D" is merely re-phrasing of "a receptor binding loop based on the receptor-binding loop 1, 2 or 3 of VEGF-D". Similarily, the phrase "first linking group at one end of the core sequence and second linking group at the other end of the core sequence" is merely rewording for clarity purpose. See original claims 19 and 33. Likewise, the phrase "deleting at least one amino acid from said loop prior to cyclizing the peptide" is conveyed in original claim 9 "deleting one or two internal amino acid residues from said loop fragment prior to cyclizing the peptide".

binding loop based on receptor binding loop 1, 2 or 3 of only VEGF-D. It means a receptor binding loop 1, 2 or 3 of VEGF, a receptor binding loop 1, 2 or 3 of VEGF-C, or a receptor binding loop 1, 2 or 3 of VEGF-D. Further, the specification discloses only monomeric monocyclic peptide based on VEGF-D. The phrase "a receptor-binding loop 1, 2 or 3 of VEGF, VEGF-C" has no support in the claims an the specification as originally filed. The specification discloses a monomeric monocyclic peptide inhibitor based on loop 1, 2 or 3 of VEGF-D (See on page 13 at line 27). With regard to claims 19 and 33, these claims are drawn to non-elected embodiment, dimeric bicyclic peptide. Further, the phrase "deleting at least one amino acid from said loop prior to cyclizing the peptide" is not exactly the same as "deleting one or two internal amino acid residues from said loop fragment prior to cyclizing the peptide".

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